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| APPLICATION NO.                                  | FILING DATE                          | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.      | CONFIRMATION NO. |
|--|--------------------------------------|----------------------|--------------------------|------------------|
| 10/824,656                                       | 04/14/2004                           | Jochen Franzen       | B0004/7120               | 7689             |
|  | 7590 10/08/200<br>S OF PAUL E. KUDIR | EXAMINER             |                          |                  |
| 40 BROAD STREET<br>SUITE 300<br>BOSTON, MA 02109 |                                      |                      | KAPUSHOC, STEPHEN THOMAS |                  |
|  |                                      |                      | ART UNIT                 | PAPER NUMBER     |
| ·  |                                      |                      | 1634                     |                  |
|  |                                      |                      |                          |                  |
|  |                                      |                      | MAIL DATE                | DELIVERY MODE    |
|  |                                      |                      | 10/08/2008               | PAPER            |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

|  | Application No.   | Applicant(s)          |  |  |  |  |
|--|---|-----------------------|--|--|--|--|
| Office Action Comments   | 10/824,656  | FRANZEN ET AL.        |  |  |  |  |
| Office Action Summary  | Examiner  | Art Unit              |  |  |  |  |
|  | Stephen Kapushoc  | 1634                  |  |  |  |  |
| The MAILING DATE of this communication app<br>Period for Reply   | pears on the cover sheet with the c   | orrespondence address |  |  |  |  |
| A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.  - Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b). |   |                       |  |  |  |  |
| Status   |   |                       |  |  |  |  |
| 1)⊠ Responsive to communication(s) filed on <u>27 A</u>  | ugust 2008  |                       |  |  |  |  |
|  | · · · · · · · · · · · · · · · · · · ·   |                       |  |  |  |  |
| <u> </u>   | ,—  |                       |  |  |  |  |
| . —  | Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11, 453 O.G. 213. |                       |  |  |  |  |
| closed in accordance with the practice under Ex pane Quayle, 1955 C.D. 11, 455 O.G. 215.   |   |                       |  |  |  |  |
| Disposition of Claims  |   |                       |  |  |  |  |
| 4)⊠ Claim(s) <u>1,4-8 and 11-19</u> is/are pending in the  | 4)⊠ Claim(s) <u>1,4-8 and 11-19</u> is/are pending in the application.  |                       |  |  |  |  |
| 4a) Of the above claim(s) is/are withdray  | 4a) Of the above claim(s) is/are withdrawn from consideration.  |                       |  |  |  |  |
| 5) Claim(s) is/are allowed.  |   |                       |  |  |  |  |
| 6)⊠ Claim(s) <u>1,4-8 and 11-19</u> is/are rejected.   |   |                       |  |  |  |  |
| 7) Claim(s) is/are objected to.  |   |                       |  |  |  |  |
| · · · · · · · · · · · · · · · · · · ·  | 8) Claim(s) is/are objected to.   |                       |  |  |  |  |
| are subject to restriction and/o   | r cicculon requirement.   |                       |  |  |  |  |
| Application Papers   |   |                       |  |  |  |  |
| 9)☐ The specification is objected to by the Examiner.  |   |                       |  |  |  |  |
| 10) ☐ The drawing(s) filed on is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.   |   |                       |  |  |  |  |
| Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  |   |                       |  |  |  |  |
| Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).   |   |                       |  |  |  |  |
| 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.   |   |                       |  |  |  |  |
|  |   |                       |  |  |  |  |
| Priority under 35 U.S.C. § 119   |   |                       |  |  |  |  |
| 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  |   |                       |  |  |  |  |
| ·—   | a) ☐ All b) ☐ Some * c) ☐ None of:  |                       |  |  |  |  |
|  | 1. Certified copies of the priority documents have been received.   |                       |  |  |  |  |
| 2. Certified copies of the priority documents  | 2. Certified copies of the priority documents have been received in Application No  |                       |  |  |  |  |
| 3. Copies of the certified copies of the priority documents have been received in this National Stage  |   |                       |  |  |  |  |
| application from the International Bureau (PCT Rule 17.2(a)).  |   |                       |  |  |  |  |
| * See the attached detailed Office action for a list of the certified copies not received.   |   |                       |  |  |  |  |
|  |   |                       |  |  |  |  |
|  |   |                       |  |  |  |  |
| Attachment(s)  |   |                       |  |  |  |  |
| 1) Notice of References Cited (PTO-892)  4) Interview Summary (PTO-413)  |   |                       |  |  |  |  |
| 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  Paper No(s)/Mail Date  3) Information Disclosure Statement(s) (PTO/SB/08)  5) Notice of Informal Patent Application   |   |                       |  |  |  |  |
| 3) Information Disclosure Statement(s) (PTO/SB/08)  Paper No(s)/Mail Date  5) Informal Patent Application 6) Other:  |   |                       |  |  |  |  |
| · · · · · · · · · · · · · · · · · · ·  | · <del></del>   |                       |  |  |  |  |

## **DETAILED ACTION**

Claims 1, 4-8, and 11-19 pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/27/2008 has been entered.

This Office Action is in reply to Applicants' correspondence of 8/27/2008. Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is NON-FINAL.

# Withdrawn Rejections - 35 USC § 112 1<sup>st</sup> ¶ - Written Description, New Matter

1. The rejection of claims 1, 4-8, and 11-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the introduction of new matter is **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 1<sup>st</sup> ¶ - Written Description, New Matter

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2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 4-8, and 11-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claim 1, from which 4-8 and 11-19 pending claims depend, have been amended to require, in step (e), that an electrical contact is established between a metal surface on a nanoparticle and a contact spot 'without destroying the nanoparticle'. This newly added to be an attempt to in some way limit the manner in which a metal surface from a nanoparticle makes contact with a spot. However, the specification as originally filed does not provide any basis for such a limitation. This is particularly important as the specification provides no guidance as to what is required for any nanoparticle to be considered 'destroyed', where this may indicate that no portion or the nanoparticle may be removed from the nanoparticle, or may require that no portion of the nanoparticle is in any way deformed. The structural limitations of what encompasses a destroyed nanoparticle are essential to the metes and bounds of this negative limitation, but the originally filed specification provides no support for this negative limitation.

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As such, the specification as originally filed does not appear to support the required limitation of a step of 'measuring one of a substantially constant current and a substantially constant voltage generated between the electrodes of the galvanic cell'.

# New Claim Rejections - 35 USC § 103

4. Claims 1, 4, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (2001) (as cited on the PTO-892 of 10/10/2006) in view of Jaya et al (1985) and Knoll (1999; WO 99/27367).

Wang et al teaches a method for measuring the binding of a nucleic acid analyte molecule to a probe molecule.

Regarding claim 1, Wang et al teaches providing a circuit surface having a contact spot and a metal counterelectrode (Fig 1; p.5577 – Electrode preparation), relevant to part (a). Relevant to part (b) of claim 1, Wang et al teaches the immobilization of probe molecules (Fig 1; p.5777 – Preparation of oligomers coated microspheres and analytical procedure). Relevant to parts (c) and (d), Wang et al teaches binding streptavidin coated gold particles to the analyte molecules, and binding of the analyte molecules to the probe molecules (Fig 1; p.5578, left col., Ins.5-11). Relevant to step (e), Wang et al teaches a counterelectrode that is Ag/AgCl and a nanoparticle surface that is gold, which are metals from an electrochemical series, and teaches analysis of the gold metal from the nanoparticle using potentiometer stripping analysis (PSA), where in PSA the gold is deposited on the contact spot of the circuit (which establishes electrical contact) in the presence of an electrolyte. Relevant to step

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(f), Wang et al teaches measuring electrical properties of the circuit created upon metal binding (Fig 3) and teaches that measurement allows the biding of the analyte molecule to the probe to be measured (p.5579 – Analytical performance).

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Regarding claim 8, Wang et al teaches that the gold nanoparticles are bound to the analyte after the analyte is bound to the capture probe (p.5578, left col., lns.8-11)

Wang et al does not specifically teach detection methods comprising measuring galvanic cell constant current or voltage generated between the electrodes of a galvanic cell, as required by step (f) of claim 1.

However, such measurements in a galvanic cell for the detection of metals, where Wang et al teaches a metal as part of a nanoparticle label of a nucleic acid analyte, were well known at the time the invention was made.

Jaya et al teaches a method, referred to as galvanic stripping analysis (GSA), where the presence of a metal analyte on a working electrode is detected as a galvanic cell is formed between the metal analyte and a platinum foil counter electrode (p.1443, lns.10-18; Fig. 1c; p.1450, lns. 15-18). Relevant to the required limitations of claim 1, Jaya et al teaches measuring a substantially constant voltage generated between the electrodes of the galvanic cell (p.1447, lns.1-6; Figs.2-4), where Jaya et al teaches measuring a range of voltage from the galvanic cell which includes a substantially constant voltage.

Neither Wang et al nor Jaya et al teaches probes immobilized in spatial proximity to the electronic circuits (as required by part (b) of claim 1), or probes immobilized on the circuit surface (claim 4) or a countersurface (claim 5). Neither Wang et al nor Jaya

et al teaches a method in which nanoparticles are bound to analytes before the analytes are hybridized to the capture probe (claim 7).

However, such methods for electrically-based nucleic acid detection were well known in the art at the time the invention was made.

Knoll et al teaches a method for electronic detection of the binding of analyte molecules to probe molecules. Relevant to step (b) of claim 1, Knoll teaches providing immobilized probe molecules in spatial proximity to a circuit surface having electronic circuits (see for example Fig 9 and 10).

Regarding claim 4, Knoll teaches probe molecules bound to the circuit surface (for example Fig 10).

Regarding claim 7, Knoll teaches the marker particle bound to the analyte prior to binding of an analyte to a probe (Fig 9), relevant to claim 7.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Wang et al, which use PSA techniques to measure a metal label for detection of nucleic acid binding, by using the GSA technique to detect a metal label. One would have been motivated to use the GSA methods of Jaya et al based on the teaching of Jaya et al that GSA is a rapid, simple, and versatile technique (p.1441 – Abstract) with advantages over other techniques (p.1454).

Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the techniques of Knoll in the method for measuring the binding of analytes to probes as taught by Wang et al in view of Jaya et al. One would have been motivated to use the methods of Knoll et al because Knoll et al teaches the successful deposition of conductive elements (termed 'marker particles by Knoll) using probes immobilized in spatial proximity to an electronic circuit of interest, and both Wang et al (Fig 1) and Jaya et al (Fig 1) teach that such deposition is required for the sensitive detection of analyte binding by using electrical methods including GSA (Jaya et al p.1448-1449).

## Response to remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the teachings of Wang et al, Jaya et al, and Knoll. Applicants' arguments (p.6-8 of Remarks) have been fully and carefully considered but are not found to be persuasive.

Initially it is noted that the rejection of claim 11 as amended in view of the cited prior art references of the instant rejection is withdrawn in light of the amendments, and claim 11 is rejected elsewhere in this Office Action.

With regard to the requirements of the claims in view of the teachings of the cited prior art, Applicants argue (p.8 of Remarks), that the present invention requires establishing an electrical contact without destroying the nanoparticles, whereas the prior art of Wang et al and Jaya et al require chemical dissolution of a metal analyte prior to analytical detection of that metal. The Examiner appreciates the difference between the instantly claimed methods and the particular teachings of Wang et al and Jaya et al, however the claims are rejected over the combination of teachings including the teachings of Knoll. The examiner maintains that Wang et al and Jaya et al teach

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methods for the detection of nucleic acids using metal nanoparticles and the detection of current or voltage produced by a galvanic cell. And while the movement of the metal to a contact spot is different in the instantly claimed methods as compared to the prior art of Wang et al and Jaya et al (i.e. Wang et al and Jaya et al teach chemical dissolution), the binding of metal nanoparticles to nucleic acids and the physical movement of such bound metal nanoparticles through space to specific physical locations, such as a 'contact spot', was well known in the art at the time the invention was made and is taught by Knoll as cited in the rejection. The examiner maintains that Knoll teaches movement of metal nanoparticles through space to specific physical locations without destroying the metal nanoparticle.

The rejection as set forth is **MAINTAINED**.

5. Claims 6, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (2001) (as cited on the PTO-892 of 10/10/2006) in view of Jaya et al (1985) and Knoll (1999; WO 99/27367) as applied to claims 1, 4, 7, and 8 above, and further in view of Henkens et al (2002, US Patent 6,391,558).

The teachings of Wang et al in view of Jaya et al and Knoll are applied to claims 6, 18, and 19 as they were previously applied to claims 1, 4, 7, and 8.

Regarding claim 6, Knoll teaches probe molecules immobilized to an electrode surface, and analyte molecules affinity bound (e.g. antibody-antigen, Fig 5; DNA:DNA / probe:analyte hybridization) to the probe molecules, and Wang et al teaches biotin:avidin immobilization of a probe.

Wang et al in view of Jaya et al and Knoll does not particularly require that the immobilized probe is bound by a covalent bond (claim 6), or provide any particular details regarding the binding of the nanoparticle to the analyte molecule (claims 18 and 19).

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Henkens et al teaches methods for the detection of nucleic acids using electrodes comprising immobilized probes, as well as analyte molecules labeled with detectable reporters.

Regarding claim 6 Henkens et al specifically teaches that capture probes may be covalently bound to an electrode (col.45 lns.16-25).

Regarding claims 18 and 19, Henkens et al teaches the PCR amplification of a analyte DNA molecule using primers modified at the 5' end, and gives the examples of fluorescein and biotin labeled primers (col.21 ln.60 - col 22. ln.4). Henkens et al indicates that the resulting labeled PCR product may be attached to a reporter molecule by an interaction between the label from the PCR primer and a binding partner for the label of the primer. Relevant to claim 18, Henkens et al teaches the biotin:avidin binding pair, as well as labeling a PCR product using a biotinylated primer, and binding of the labeled PCR product to a avidin-gold biding partner (for example col.5 lns.25-35, col.43 ln.55). Relevant to claim 19, Henkens et al particularly teaches biding of a fluorescein-labeled PCR product to an anti-fluorescein HRP conjugate.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the nucleic acid probe immobilization methods of Henkens et al in the electrode based analysis methods of Wang et al in view

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of Jaya et al and Knoll. One would have been motivated to do so based on the assertion of Henkens et al that covalent attachment of a probe is a preferred method (col.45 lns. 16-25). It would further have been obvious to use the probe:reporter binding method of Henkens et al to accomplish the marker particle:analyte binding of Wang et al in view of Knoll et al. One would have been motivated to do so because Henkens et al teaches that such methods can be used to attach a variety of different molecules (including colloidal gold which is similar to the description of marker particles by Knoll) to nucleic acid for analysis.

# **Response to Remarks**

Applicants argue (p.9 of Remarks), that Henkens does not disclose the formation of a galvanic cell by intact nanoparticles. However, the limitations of the claims which require formation of a galvanic cell are taught by Jaya et al, and the limitations of the claims which require intact nanoparticles moved to a specific physical location are taught by Knoll, as addressed previously in this Office Action. In the rejection, Henkens is not relied upon for any teachings of galvanic cell formation by intact nanopaticles.

6. Claims 5, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (2001) (as cited on the PTO-892 of 10/10/2006) in view of Jaya et al (1985) Knoll (1999; WO 99/27367), as applied to claims 1, 4, 7, and 8 above, and further in view of Wohlstadter et al (2001, US Patent 6,207,369).

As discussed in detail in the rejection of claims 1, 4, 7, and 8 earlier in this Office Action, Wang et al in view of Jaya et al and Knoll teaches all of the required limitations of claim 1 from which claims 5, 11 and 12 depend.

Furthermore, relevant to claim 11, Knoll teaches that the marker particles may be conductive (col.14 Ins.5-9), thus they are electrically conductive molecules.

Wang et al in view of Jaya et al and Knoll does not specifically teach probe molecules bound to a countersurface positioned opposite the circuit surface (claim 5), or establishing electrical contact by conductive molecules other than the nanoparticles (claim 11) and specifically use of polyene molecules to conduct an electrical signal (claim 12).

Regarding claim 5, Wohlstadter et al teaches methods of using several configurations of electrode-based devices in which the portion of the device where the analyte is collected (termed in the reference the 'binding domain') is on a surface opposite from an electrode (see for example Fig. 21 and Fig. 37).

Regarding claims 11 and 12, Wohlstadter et al teaches the use of a linking chain to ensure low resistance of electron transfer from the electrode, and specifically teaches the use of a polyacetylene chain (col.39 lns.53-63), which is of the polyene class.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have performed the electronic detection methods of Wang et al in view of Jaya et al and Knoll using a probe binding area on a countersurface opposing an electrode. One would have been motivated to do so based on the teachings of Wohlstadter et al that in such a configuration the electrode can be

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protected during the binding reaction from the sample by a physical barrier that is subsequently removed thus, preventing contamination of the electrode surface which could result in a change in its electrochemical performance (col.64 lns.1-11). One would have a reasonable expectation of success because Wohlstadter et al teaches that the binding domain of the countersurface makes contact with the electrode and carries current from the counter electrode to the working electrode (col.45 lns.9-35). It would have been further obvious to use the polyacetlyene chains of Wohlstadter et al to ensure low resistance of conductivity from the electrode to the marker particle as Wohlstadter et al teaches this use for polyacetylene chains.

## **Response to Remarks**

Applicants argue (p.9 of Remarks), that Wohlstadter et al does not disclose forming a galvanic cell and the measuring the electrical properties of that element as recited. However, the limitations of the claims which require formation of a galvanic cell are taught by Jaya et al, as addressed previously in this Office Action. In the rejection, Wohlstadter et al is not relied upon for any teachings of galvanic cell formation.

7. Claims 13, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (2001) (as cited on the PTO-892 of 10/10/2006) in view of Jaya et al (1985) and Knoll (1999; WO 99/27367), as applied to claims 1, 4, 7, and 8 above, and further in view of Fish (2002, WO 02/054052 A1).

As discussed in detail in the rejection of claims 1, 4, 7, and 8 earlier in this Office Action, Wang et al in view of Jaya et al and Knoll teaches all of the required limitations of Claim 1, from which claims 13, 16, and 17 depend.

Relevant to claim 16, Knoll specifically teaches that the marker particles may be magnetic (see for example col.4 lns.10-24).

Relevant to claim 17, Knoll teaches that the marker particles may be dendrimers (col.14 lns.2-3), which are protrusions.

Wang et al in view of Jaya et al and Knoll does specifically teach a requirement of nanoparticles touching a contact spot, though Wang et al and Jaya et al both teach the requirement of the metal label contacting an electrode.

Fish teaches the detection of analytes using an electrode-based method wherein an opposing surface with an electrode is moved to make contact with an electrically readable particle that is bound to and analyte, where the analyte is bound to an immobilized probe (see for example Fig 1, p.14-18). Regarding claim 13, Fish specifically teaches that pressure is applied to the particle (p.16 last two lines) and that the bound particles make contact with the electrode (p.17 lns.7-8).

Regarding claim 16, Fish teaches that a countersurface may be moved in order to create a physical contact between an electrode (which is a contact spot) and an electrically readable particle, and also teaches that the probes may be attached to a contact spot and that movement of the countersurface causes the particles to make contact with the contact spot (see for example Fig 13 and page 28).

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Additionally relevant to claim 17, Fish teaches that an electrode may be rough and have sharp edges and vertices to make electrical contact (p.42), thus teaching a circuit surface with electrically conductive protrusions.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have performed the electrode-based analyte detection method of Wang et al in view of Knoll by incorporating the countersurface movement taught by Fish to make contact between a particle and an electrode. One would have been motivated to do so based on the teachings of Fish that such methods allow accurate electrochemistry to be performed quickly at a low cost (p.7), and the teaching of the methods of Wang et al requiring contact between the element of the nanoparticle and the electrode. One would have had a reasonable expectation of success because Wang et al in view of Knoll teaches that the electrode-based method can be used as a multi-step process separating the steps of particle transport and electrode binding (Knoll et al at col. 5 lns.62-67).

## Response to Remarks

Applicants argue (p.9-10 of Remarks), that Fish detects the presence and quantity of the analyte molecules by measuring electrical changes in a cell, and does not disclose forming a galvanic cell and the measuring the electrical properties of that element as recited. However, the limitations of the claims which require formation of a galvanic cell are taught by Jaya et al, as addressed previously in this Office Action. In the rejection, Fish is not relied upon for any teachings of galvanic cell formation

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8. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (2001) (as cited on the PTO-892 of 10/10/2006) in view of Jaya et al (1985) and Knoll (1999; WO 99/27367) and Fish (2002, WO 02/054052 A1), as applied to claims 13, 16, and 17 above, and further in view of Wohlstadter et al (2001, US Patent 6,207,369).

The teachings of Wang et al in view of Jaya et al, Knoll, and Fish are applied to claims 14 and 15 as they were previously applied to claims 13, 16, and 17.

Wang et al in view of Jaya et al, Knoll, and Fish teaches an electrode-based method of analyte detection wherein marker particles bind to analyte molecules and contact between the marker particle and a contact spot is made by the nanoparticles touching the contact spot.

Regarding claim 15, Wang et al a method in which a gold nanoparticle binds to a target oligonucleotide wherein the target oligonucleotide has hybridized to a probe oligonucleotide immobilized to a solid support (Fig 1; p.5577, left col., Ins.5-10). The method of Wang et al includes a step of dissolution of the gold nanoparticle from the analyte molecule prior to detection of the gold nanoparticle at an electrode.

Wang et al in view of Jaya et al, Knoll, and Fish does not specifically teach that the analyte molecule:particle complex is located on a surface opposite the circuit surface.

Wohlstadter et al teaches methods of using several configurations of electrodebased devices in which the portion of the device where the analyte is collected (termed

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in the reference the 'binding domain') is on a surface opposite from an electrode (see for example Fig. 21 and Fig. 37).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the opposed binding and electrode surfaces taught by Wohlstader et al in the electrode-based analyte detection method of Wang et al in view of Jaya et al, Knoll, and Fish. One would have been motivated to do so based on the teachings of Wohlstadter et al that in such a configuration the electrode can be protected during the binding reaction from the sample by a physical barrier that is subsequently removed thus, preventing contamination of the electrode surface which could result in a change in its electrochemical performance (col.64 Ins.1-11).

Regarding the limitations of claim 15, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the dissolution of a gold microparticle from a bound analyte molecule as taught by Wang et al as a detectable nanoparticle in the electrode-based analyte detection method of Knoll in view Fish and Wohlstadter et al. One would have bee motivated to use such a method because Wang et al teaches the sensitivity ((p.5581, left col., Ins.13-16) and adaptability (p.5581, right col., Ins.17-19) of such a technique. Incorporating the methods of Wang et al into the teachings of Knoll et al would result in the use of a magnetic field to move an electrically conductive and magnetic marker particle to an electrode after separation of the particle from a particle:analyte:probe complex.

## **Response to Remarks**

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Applicants' arguments (p.10 of Remarks) concerning the deficiency of the references with regard to the teaching of formation of a galvanic cell have been addressed previously in this Office Action.

### Conclusion

#### 9. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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